REMARKS

The Office Action

Claims 83-109 are pending. Claims 83, 84, 88-96, 98-104, and 107-108 stand rejected under 35 U.S.C. § 102(b). Claim 85, 86, 87, 97, 105, 106, and 109 stand rejected under 35 U.S.C. § 103. Each of the rejections is addressed in detail below.

Amendments to the Claims

Independent claim 83 has been amended to recite the limitation that the negative selection marker, a positive selection marker, and reporter gene are all integrated into the genome of at least one cell and responsive to one or more endogenous regulatory elements in the cell after the nucleic acid is contacted with a cell. This linkage of *all three elements* to endogenous regulatory elements of the host cellular gene is advantageous because it allows for rapid development of cellular assays in which activity of the regulated genetic site can be measured quantitatively. Having the positive selection marker responsive to one or more endogenous regulatory elements allows for selection of cells in which the nucleic acid has integrated into an active genetic site. Having the negative selection marker responsive to one or more endogenous regulatory elements allows for the separation of cells in which the active genetic site is a regulated site from the cells in which the active genetic site is constitutively active (i.e., a housekeeping gene regulatory element). Having the reporter gene responsive to one or more endogenous regulatory elements allows for a quantitative read-out of the activity at the host cell

regulated active genetic site, for example, after stimulation with an agent that stimulates activity of the regulatory element. Accordingly, claim 83 and dependent claims 84-96 feature novel nucleic acids and vectors having three selection markers in one nucleic acid all integrated into the genome of a cell and responsive to one or more endogenous regulatory elements in that cell.

Independent claims 97 and 109 have been amended to recite the limitation that the positive selection marker, negative selection marker, and the nucleic acid encoding the transactivator polypeptide are all integrated into the genome of at least one host cell and responsive to one or more endogenous regulatory elements in the cell. As described at page 10, line 27, to page 11, line 3 of the specification, having the transactivator polypeptide responsive to a regulatory element in the cell allows for a feedback process whereby activity at the endogenous host cell regulatory element stimulates activation of the transactivator protein which can then stimulate another nucleic acid having a reporter element that is downstream of a promoter that is responsive to the transactivator protein.

Support for these amendments can be found throughout the specification and the claims, for example, at page 6, lines 15-23 and lines 29-31; page 9, lines 28-30; page 11, lines 14-19; page 12, lines 2-3 and lines 23-27; page 13, lines 7-12; page 32, lines 13-16; page 38, line 27 to page 39, line 16, and in Figure 5. No new matter is added by these amendments.

Rejections under 35 U.S.C. § 102(b)

Claims 83, 84, 88-96, 98-104, and 107-108 are rejected under 35 U.S.C. § 102(b) for anticipation by Baetscher et al., U.S.P.N. 5,922,601 (hereafter referred to as "Baetscher").

Claims 83, 84, and 88-96

The Examiner has maintained the rejection of claims 83, 84, and 88-96 on the basis that Baetscher describes gene trap constructs that generally include a splice acceptor, an IRES, and a promoterless protein coding sequence encoding a positive and negative selection trait, which can then be placed in a viral construct that contains LTR elements and a selectable or assayable marker. Applicant respectfully submits that the Examiner has mischaracterized Baetscher and that this rejection should be withdrawn.

Independent claim 83 and dependent claims 84-96 all feature a nucleic acid including a splice acceptor site and a cassette that includes a negative selection marker, a positive selection marker, and a reporter gene where both markers and the reporter gene are integrated into the genome of at least one cell and responsive to one or more endogenous regulatory elements in the cell after the nucleic acid is contacted with a cell. This linkage of all three elements to endogenous regulatory elements of the host cellular gene is particularly advantageous because it allows for rapid development of cellular assays in which activity of the regulated genetic site can be measured quantitatively.

In making the rejection, the Examiner, on pages 3 to 5 of the Office Action, recites

the general formula of the constructs taught by Baetscher. Of these, the only constructs that include three markers, namely, a negative selection marker, a positive selection marker, and a reporter gene are the ones that are placed within the context of a retroviral vector. As described by the Examiner in the Office Action, the Baetscher constructs have the following formulas:

> Splice acceptor—IRES—positive selection—negative selection—STOP—*promoter*—reporter;
>
> Splice acceptor—IRES—Neo-HSV-TK—STOP—*promoter*—Ampicillin; and
>
> Splice acceptor—IRES—reporter—negative marker—STOP—*promoter*—positive marker. (Emphasis added.)

In all of Baetscher's constructs there is a promoter within the construct that drives expression of either the reporter or the selectable marker. Applicant's claimed constructs require that all three elements (i.e., the selectable markers and the reporter gene) are under the control of an endogenous regulatory element in the host cell. Such a construct is never taught by Baetscher.

In response to Applicant's previous arguments, the Examiner states that although claim 83 included a nucleic acid having a splice acceptor site and a cassette including a negative selection marker, a positive selection marker, and a reporter gene operably

linked to regulatory elements of a host cellular gene, the term "operably linked" as defined in the specification can mean that the markers are encoded by the same transcription unit. The Examiner concludes that Baetscher's teaching of a construct having a "splice acceptor site—IRES—positive selection—negative selection—reporter, all under the same endogenous promoter of "a host cellular gene" still anticipates claim 83, because the same transcription unit can be used for the selection markers and the reporter gene." (Office Action, page 6).

For clarity, Applicant has amended independent claims 83 and 97 to recite the limitation that the selection markers, reporter gene, and nucleic acid encoding the transactivator protein are integrated into the genome of at least one host cell and responsive to one or more endogenous regulatory elements in the cell.

Turning to the Examiner's characterization of Baetscher, Applicant submits that the Examiner's characterization of Baetscher on page 6 of the Office Action is inaccurate and inconsistent with the statements about Baetscher on the previous pages of the Office Action. On page 6 of the Office Action, the Examiner states that Baetscher teaches a construct having a splice acceptor site—IRES—positive selection—negative selection—reporter, all under the same endogenous promoter of "a host cellular gene." This characterization of Baetscher is erroneous. Baetscher never teaches a construct where all of the selection markers and reporter gene are under the control of a host cellular promoter. In fact, as acknowledged by the Examiner on page 4 of the Office Action, "in order to get expression of the reporter, a promoter element must be operatively linked to

the reporter gene." (Office Action, page 4). As described above, all of Baetscher's constructs that include two selection markers and a reporter gene include a promoter element regulating expression of one of the genes, a fact which is acknowledged by the Examiner throughout the Office Action.

In sum, none of the constructs described by Baetscher include a negative selection marker, a positive selection marker, and a reporter gene where all three elements are integrated into the genome of a host cell and responsive to one or more endogenous regulatory elements in the host cell as recited in claim 83, as presently amended. Therefore, Baetscher does not anticipate independent claim 83, or dependent claims 84 and 88-96, each of which include all the limitations of claim 83, and this rejection should be withdrawn.

Claims 98-104 and 107-108

Claims 98-104 and 107-108 are rejected under 35 U.S.C. § 102(b). Applicant submits that this basis for the anticipation rejection is in error.

The Examiner acknowledges that claims 86, 97, and 109 are novel over Baetscher because Baetscher does not teach a transactivator incorporated into the nucleic acid cassette or vector (Office Action, pages 6-7), a limitation found in claims 86, 97, and 109. Claims 98-104 and 107-108 all depend from claim 97 and, by definition, include the limitation that the construct includes a nucleic acid encoding a transactivator incorporated into the nucleic acid cassette or vector. Therefore, Applicant submits that, as for claim

97, dependent claims 98-104 and 107-108 are novel over Baetscher and that the rejection of claims 98-104 and 107-108 under 35 U.S.C. § 102(b) should be withdrawn.

Rejection of claims 85, 86, 87, 97, 105, 106, and 109 under 35 U.S.C. § 103

Claims 85, 86, 87, 97, 105, 106, and 109 stand rejected under 35 U.S.C. § 103 for obviousness over Baetscher in view of MPEP § 2144.04 (VI)(C), Zambrowicz et al., U.S.P.N. 6,436,707 (hereafter referred to as "Zambrowicz"), or Massie et al. (*J. Virology* 72:2289-2296 (1998); hereafter referred to as "Massie"). This rejection should be withdrawn because the references, either alone or combined, fail to teach or suggest all of the claim limitations of claims 85, 86, 87, 97, 105, 106, and 109.

Claim 85

Claim 85 is rejected for obviousness over Baetscher in view of MPEP § 2144.04 (VI)(C). The Examiner has maintained the rejection because, according to the Examiner, Baetscher teaches all of the elements of the claimed nucleic acids and the cited passage of the MPEP § 2144.04 (VI)(C) states that the rearrangement of parts is an obvious matter of design choice unless the variation modifies the operation of the device. Applicant respectfully submits that claim 85, which depends from claim 83, includes limitations that are not taught by Baetscher, regardless of order or orientation, therefore, claim 85 is not obvious over the combination of Baetscher with MPEP § 2144.04 (VI)(C).

As described above, claim 85 includes the following: a nucleic acid molecule having a positive selection marker, a negative selection marker, and a reporter gene all of which are integrated into the genome of at least one host cell and responsive to one or more endogenous regulatory elements in the cell. Baetscher does not teach a vector having all three elements responsive to an endogenous host cell regulatory element. The citation of MPEP § 2144.04 (VI)(C), with respect to the arrangement of elements in the claims, does not apply to the claims as currently amended because the elements themselves are not taught by Baetscher, regardless of the arrangement. Thus, the obviousness rejection, as it pertains to claim 85, should be withdrawn.

Claims 87 and 106

Claims 87 and 106 are rejected for obviousness over Baetscher in view of Zambrowicz. In maintaining the rejection, the Examiner states that Baetscher teaches all of the elements of the claimed nucleic acids, as described in the § 102(b) rejection, but not the specific use of recombinase sequences in their nucleic acids. The Examiner states that Zambrowicz teaches the construction of gene trap vectors that include splice acceptor sites, IRES elements, and positive/negative selectable marker genes and further teaches the use of recombinase sites within the gene trap cassette. Therefore, the combination of Baetscher with Zambrowicz would, according to the Examiner, render claims 87 and 106 obvious.

Claim 87 depends from claim 83 and features all of the elements of claim 83, as described above, and further includes a recombinase signal sequence. Claim 106 depends from claim 97 and features all of the elements of claim 97 and further includes a recombinase signal sequence. As described in detail above in response to the § 102(b) rejection, Baetscher does not teach all of the limitations of independent claims 83 or 97, or the claims that depend therefrom, and Zambrowicz fails to remedy this deficiency. Zambrowicz's teaching of the inclusion of a recombinase signal sequence does not remedy the fundamental deficiency of Baetscher, namely, a failure to teach a nucleic acid construct where the positive and negative selection markers and the reporter gene are all integrated into the genome of at least one host cell and responsive to one or more endogenous regulatory elements in the cell. Thus, the obviousness rejection of claims 87 and 106 should be withdrawn.

Claims 86, 97, 105, and 109

Claims 86, 97, 105, and 109 are rejected for obviousness over Baetscher in view of Massie. In setting forth the rejection, the Examiner states that Baetscher teaches all of the elements set forth in the claims with the exception of a transactivator polypeptide incorporated into a cassette or vector but that Massie teaches a cassette and a vector that includes the tetracycline transactivator. Therefore, according to the Examiner, the ordinary skilled artisan would have

combined the teachings of Baetscher with Massie to arrive at the present invention. Applicant respectfully disagrees.

Claim 86, which depends from claim 83, features all of the elements of claim 83, as described above, and further includes a nucleic acid encoding a transactivator polypeptide that is incorporated into the cassette or vector.

Claims 97 and 105 each include a positive selection marker, negative selection marker, and a nucleic acid encoding the transactivator polypeptide, all of which are integrated into the genome of a host cell and responsive to one or more endogenous regulatory elements in the cell.

Claim 109 features a cell that includes a cassette having a positive and negative selection marker and a nucleic acid segment encoding a transactivator polypeptide, which is incorporated into the cassette. The cassette is integrated into the genome of the cell and the positive and negative selection markers and the nucleic acid segment encoding a transactivator polypeptide are responsive to one or more endogenous regulatory elements in the cell. The cell also includes a nucleic acid that includes a promoter operably linked to an element that is directly responsive to the transactivator polypeptide.

As acknowledged by the Examiner, Baetscher does not describe any constructs or cells that include a transactivator polypeptide. As is the case for the previous claims, Baetscher does not teach all of the elements of the claims and Massie fails to remedy this deficiency. Massie describes adenovirus vectors that include a transactivator polypeptide, however, none of Massie's constructs include

a transactivator polypeptide that is *integrated into the genome of a host cell and responsive to one or more endogenous regulatory elements in the cell.*

Massie teaches the use of a tetracycline-regulated promoter to generate recombinant adenoviruses to express proteins that are cytotoxic or that interfere with adenovirus replication. Massie describes the use of the recombinant adenovirus to produce the toxic proteins by either coexpression of the virus with a second vector that expresses the transactivator (tTA) under the control of a CMV promoter (see page 2292) or by transducing the virus into cell lines that already stably express the tTA under the control of the CMV promoter (see page 2290, Materials and Methods). Massie does not teach a vector or cell in which the expression of the tTA is regulated by an endogenous regulatory element in the host cell. The very purpose of Massie is to maximize expression of the tTA not to connect tTA expression to endogenous elements within the host cell that may or may not be activated by stimulatory elements. Massie does not teach any type of construct or cell for examining host cell regulatory element controlled expression of the tTA protein or the selectable markers in the vector. Therefore, taken alone or together, the references fail to teach or suggest all of the limitations of claims 86, 97, 105, and 109 and the rejection of these claims for obviousness should be withdrawn.

CONCLUSION

Applicant submits that the claims are now in condition for allowance and such action is respectfully requested.

Enclosed is a Petition to extend the period for submitting an appeal brief pursuant to the Notice of Appeal filed on November 20, 2006, for five months to and including June 20, 2007.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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